

11:30

749-5 Clinical Significance of Reduced Glucose Uptake in Myocardial Regions With Preserved Blood Flow in Patients With Coronary Artery Disease

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Hibernation is a condition characterized by a chronic reduction of perfusion and function with preserved tissue viability and is expressed as a perfusion-metabolism "mismatch" on PET imaging. However, patients (Pts) with CAD may occasionally exhibit a pattern of reduced glucose uptake in regions with preserved blood flow ("reversed" mismatch, RMm). The purpose of this study was to examine the clinical, functional, and arteriographic correlates of a RMm pattern in Pts with CAD. Regional perfusion (MP) and glucose uptake (after oral glucose loading) were evaluated quantitatively in 15 Pts with CAD and chronic LV dysfunction (LVEF: $30 \pm 9\%$), and in 10 healthy volunteers with N-13-ammonia, F-18-deoxyglucose and PET. Oxidative metabolism (MVO2) was also evaluated with PET in 7 of 15 Pts by mono-exponential fitting of the C-11-acetate clearance rate. Surface ECG did not demonstrate Q wave infarction in 13/15 "reversed" mismatch regions and showed LBBB in the remaining 2. Resting MP in RMm regions was similar to that in normal myocardium ($81 \pm 8\%$ vs $85 \pm 3\%$, P-NS), while glucose uptake ($61 \pm 20\%$ vs $93 \pm 7\%$, $P < 0.001$) and MVO2 ($86 \pm 8\%$ of normal, $P < 0.01$) were significantly reduced. Systolic wall motion, from contrast left ventriculography, of myocardium with a RMm pattern was hypokinetic in 8 of 15 regions and akinetic-dyskinetic in 7 regions. The arteriographic stenosis severity of coronary arteries supplying RMm segments was 100% with TIMI 2-3 collateral flow in 6 of 15 regions, $> 90\%$ in 4, $> 70\%$ in 3, and $> 50\%$ in 2. Thus, the pattern of "reversed" mismatch was associated with regional contractile abnormalities in myocardium with no evidence of Q wave infarction supplied by highly stenosed coronary arteries. This perfusion-contraction "uncoupling" with decreased metabolism agrees with experimental observations post reperfusion and suggest that "chronic" stunning may be the underlying mechanism.

11:45

749-6 Resting Technetium-99m Tetrofosmin Myocardial SPECT With and Without Attenuation Correction for Detecting Viable Myocardium: Comparison With FDG-PET

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The lack of attenuation correction (AC) is one of the major limitations for quantitative analysis of conventional SPECT images. Multihead SPECT allows for simultaneous transmission and emission imaging. The aim of this study was to evaluate the significance of attenuation correction for identifying viable myocardium with Tc-99m tetrofosmin (TFM), a newly introduced myocardial perfusion imaging tracer, compared to FDG-PET. 10 patients with coronary artery disease were studied (mean LVEF 32%). All underwent resting TFM SPECT and FDG-PET imaging. The simultaneous transmission and emission scan was performed using a triple-headed SPECT system (Siemens, Multi-SPECT3) with a collimated Am-241 linesource. The SPECT data were reconstructed with and without AC. The left ventricular myocardium was divided into 9 segments and the mean regional activities relative were calculated for each segment using semi-quantitative polar map approach for SPECT and PET. The regional FDG uptake was normalized to the region with the maximal TFM uptake on AC images. A closer correlation of regional activities was observed between TFM with AC and FDG-PET ($r = 0.66$, $p < 0.001$) than between TFM without AC and PET ($r = 0.50$, $p < 0.001$). When a threshold level of 50% was used for both tracers as an index for viable myocardium, 47% of TFM defects ($< 50\%$ of peak activity) with AC were considered to be non-viable by PET. Without AC, only 30% of severe TFM defects were considered to be non-viable by PET. Thus, AC appears to enhance the identification of viable myocardium with TFM. However, resting TFM imaging appears to underestimate myocardial viability even with AC as compared to FDG-PET.

750

Thrombosis, Atherosclerosis, and Vascular Biology: Gene Transfer and Molecular Mechanisms

Tuesday, March 26, 1996, 10:30 a.m.—Noon
Orange County Convention Center, Room 230C

10:30

750-1 Homocyst(e)ine Decreases Cell Redox Potential in Vascular Smooth Muscle Cells

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Homocyst(e)ine (HCY) is an independent risk factor for atherothrombosis that has been shown to induce endothelial cell injury, yet paradoxically increase vascular smooth muscle cell proliferation. Since these effects appear to be mediated by hydrogen peroxide (H_2O_2) generated during the oxidation of HCY, we hypothesized that HCY, acting as a source of oxidative stress, would decrease cell redox potential [defined as the ratio of intracellular reduced glutathione (GSH) to oxidized glutathione (GSSG)]. To test this hypothesis, rat aortic smooth muscle cells (VSMC) were grown to confluency and exposed to either media alone (control), media containing 500 μM HCY, media containing 500 μM HCY and 500 U/ml catalase, or media containing 500 μM H_2O_2 . After a four-hour incubation, intracellular GSH and GSSG were determined using HPLC with electrochemical detection to measure GSH and a spectrophotometric assay to measure GSSG. The intracellular concentration of GSH and GSSG is expressed as a ratio for each treatment group (GSH/GSSG). Compared with control (164.9 ± 41.4), treatment with 500 μM H_2O_2 substantially decreased the ratio of GSH/GSSG (4.0 ± 3.5 , $p < 0.003$ vs. control). Treatment with 500 μM HCY alone decreased GSH/GSSG by more than 49% (80.3 ± 24.2 , $p < 0.05$ vs control). The addition of 500 U/ml catalase to the media containing 500 μM HCY partially attenuated HCY's effect on the redox ratio (107.3 ± 33.5 , $p = NS$ vs control). These results indicate that H_2O_2 , as a potent source of oxidative stress, mediates HCY's adverse effect on cellular redox potential. Since H_2O_2 stimulates VSMC proliferation, our data suggest that the mitogenic effect of HCY on VSMC is mediated by a dramatic, H_2O_2 -induced decrease in cell redox state.

10:45

750-2 Adenoviral Gene Transfer to Venous Bypass Grafts and Native Vessels: A Quantitative Study

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Vein graft (VG) failure, the major limitation of coronary artery bypass surgery, may be amenable to gene therapy approaches. VG represent ideal potential targets for gene therapy, since the vein is available for ex-vivo gene transfer intra-operatively. We examined the relative efficiency of adenoviral gene transfer in VG with that in native vessels, using a rabbit jugular vein-carotid artery venous bypass graft model. To compare gene transfer in VG with ungrafted vessels, we carried out in-vivo gene transfer of β -Galactosidase (β -Gal) to VG (prior to implantation), to native jugular veins (JV), and to carotid arteries (CA), in the same animal. For virus delivery we used luminal dwell with viral titer of 1×10^9 pfu/ml for 30 minutes. β -Gal expression was determined both by x-gal staining of vessels and by direct measurement of β -Gal protein in vessel extracts using a β -Gal ELISA.

Results: A total of 24 vessels from 6 rabbits were studied for β -Gal expression 3 days after infection. Segments of untransfected aorta (Ao) were used as controls. All gene-transferred vessels stained blue with x-gal. No blue cells were seen in uninfected aorta. β -Gal protein levels per mg of vessel protein are shown in the table.

Vessel Type	n	β -Gal (ng/mg protein) (mean \pm SD)
CA	6	918 ± 417
JV	6	1164 ± 1082
VG	6	$129 \pm 83^{**}$
Ao	6	$0.3 \pm 0.3^{**}$

^{**}denotes $p < 0.05$ vs. JV.

Conclusions: Gene transfer to rabbit CA and JV is highly efficient and generates high levels of β -Gal expression (0.1% of total protein). However, following bypass grafting, β -Gal levels in VG are 7-fold lower than in control JV. The reduction in protein levels in VG compared with ungrafted vessels may have important implications for gene transfer: as a therapeutic approach in VG.